REMARKS/ARGUMENTS

I. Status of the claims

Claims 1-68 are pending. Claims 41-50 have been withdrawn from consideration as drawn to a non-elected invention and claims 51-68 have been added by the present amendment.

II. The Amendments Herein

No new matter has been added by the present amendments.

The specification has been amended to provide priority information. Further, the specification has been amended to state the number of a patent issued from an application referenced in the text, and the text has been amended to avoid the creation of an active hyperlink when the application is published, all as requested by the Action.

The amendments to the claims likewise add no new matter. Claims 1, 27, and 33 have been amended to add a recitation that the polypeptide does not differ from the parental antibody with respect to amino acids in the CDR that are not encoded by a codon with a nucleotide not in a hot spot motif. Polypeptides in which amino acids encoded by codons with nucleotides within a hot spot are mutated without mutating an amino acid not encoded by a codon with nucleotides not within a hot spot are supported throughout the specification, including page 22, line 33, to page 23, line 2, and Example 1. The amendment to claim 21 is supported throughout the specification, including page 29, lines 3-5. The amendments to claim 22 correct a typographical error and improve its clarity. Claim 35 has been amended to recite specific mutations by which the respective antibodies differ from SS. Claim 40 has been amended to add the period missing at the end of the claim.

New claims 51-68 track the original claims, but are more specifically drawn to antibodies with improved affinity compared to SS antibody. The new claims are supported by the claims as originally presented.

III. The Office Action

The Action rejects claims 1-40 on a variety of grounds. Applicants amend in part and traverse all the rejections. For the Examiner's convenience, the rejections are discussed separately below, in the order in which they appear in the Action.

A. Objections to Informalities.

1. Abstract of the Disclosure.

The Action asserts that the specification does not contain an abstract of the invention and requires submission of an abstract on a separate sheet. Action, at page 3.

Applicants respectfully observe that the application does in fact contain the required abstract. As in all published PCT applications, the abstract is printed on the face page of the application, at item (57), directly under the printed figure. It therefore appears that the Action's objection is grounded on an inadvertent failure to note the presence of the abstract. Reconsideration and withdrawal of the objection is respectfully requested.

For the sake of good order, Applicants also note that the abstract published in the PCT application meets U.S. filing requirements. Abstracts in PCT applications are filed by the applicants on a separate sheet following the claims (see, MPEP §1826, page 1800-39, left column), but the international authorities then print them on the first page. Applicants understand that, pursuant to the Patent Cooperation Treaty, the Office must accept applications meeting PCT requirements as meeting U.S. filing requirements. The published PCT applications have, accordingly, been uniformly accepted by the Office as meeting the requirements of U.S. national stage applications. The Action articulates no reason why this procedure, which has been uniformly applied to national phase applications under 35 U.S.C. § 371, is suddenly no longer acceptable with respect to the present specification.

2. Correction of priority information.

The Action states that the priority information in the first paragraph of the specification should be amended to reflect the correct priority of the application. Action, at page 3. The requested amendment has been made.

3. Correction of application information.

The Action states that information regarding an application cited on page 12 should be updated to reflect issuance of the patent stemming from that application. Action, at page 3. The requested amendment has been made.

4. Correction of embedded hyperlink.

The Action notes the presence of a hyperlink, and requires its deletion so that an active hyperlink will not be present when the application is published. Action, at page 3. The text has been amended to avoid creation of an active hyperlink.

B. Rejections Under 35 U.S.C. § 112, Second Paragraph

1. Rejection of Claim 21

Claim 21 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. According to the Action, it is unclear whether the polypeptide of claim 1 is expressed by a bacteriophage or whether the polypeptide comprises "just any surface protein of a bacteriophage." Action, at page 3. The claim has been amended to clarify that it refers to the polypeptide of claim 1 when expressed as a surface protein of a bacteriophage.

2. Rejection of Claims 1, 27, and 33.

Claims 1, 27, and 33 are rejected under §112, second paragraph, as indefinite for not reciting whether the nucleotide in a hot spot motif in the codon encoding an amino acid is in the parental sequence or in the mutated sequence. The claims have been amended to clarify that the nucleotide in the hot spot motif in the codon encodes the amino acid in the parental antibody. Applicants respectfully submit this makes it clear the nucleotide is in a hot spot encoding the original, parental antibody sequence.

C. Rejections Under 35 U.S.C. § 112, First Paragraph

1. Rejection of claims 6 and 22

Claims 6 and 22 are rejected under §112, first paragraph, as allegedly not enabled. According to the Action, the claimed "biological materials" have not been shown to be known and readily available to the public and reproducible from the written description. The Action further alleges that practice of the invention cannot be performed without undue experimentation. Action, at pages 4-7. The Action alleges that support for this proposition is provided by a citation to Paul's Fundamental Immunology (1993) at page 242, which indicates that very different VH chains can combine with the same VK chain to provide antibody binding sites with very similar properties. Action, at page 5. The Action acknowledges that there is sufficient guidance to make antibodies SS1, D8, C10, and E4, provided antibody SS is publicly available. *Id.*, at page 7. Applicants amend in part and traverse.

As an initial matter, Applicants observe that the deposit requirement was created in relevant part to handle situations relating to biological materials that could not be adequately described in writing. With the advent of improved methods of sequencing and recombinant techniques, it is relatively uncommon for a deposit to be required to enable a claim. A study of claims 6 and 22 reveals that no deposit is required here.

The Examiner's attention is respectfully drawn to Figure 1 of the specification. Figure 1 sets out the sequence of the variable regions (Fvs) of the light and heavy chains of the SS antibody, and specifies the sequences of the hypervariable, or "complementarity determining regions (CDRs)" of the SS antibody. As stated in Kuby Immunology (Goldsby et al. eds.), W.H. Freeman and Co., NY (4th Ed. 2000), at page 89, "[t]he hypervariable regions form the antigen-binding site of the antibody molecule." Figure 1 therefore provides all the information needed by a person of skill in the art to create the polypeptides claimed in claims 6 and 22 as presented. The practitioner can readily construct antibodies meeting the recitations of the claims using the sequence of the Fvs of the SS antibody, as set forth in Figure 1, or of the CDRs of the SS antibody, as recited in claim 22 as amended.

Applicants respectfully remind the Examiner that "[the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in

the patent coupled with information known in the art without undue experimentation.". MPEP § 2164.01, *quoting, United States v. Telectronics, Inc.*,857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Further, the Examiner's attention is respectfully drawn to MPEP § 2173.02. Section 2173.02 instructs the Examining Corps that claim language "must be analyzed, not in a vacuum but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level skill in the pertinent art at the time the invention was made." As noted, the content of this particular application disclosure includes Figure 1, which sets forth specific sequences for the VH and VL chains of the SS antibody, as well as for the CDRs. The practitioner seeking to practice the invention as claimed therefore has all the information necessary.

The enablement of the claims under consideration is not affected by the Action's citation from Paul's Immunology. The passage cited from Paul's merely shows that there may be other ways to achieve antibodies of similar affinity and specificity to a starting antibody than by mutating the CDRs. Applicants respectfully observe that the fact that other antibodies may be generated with affinity similar to that of a starting antibody by combining very different VH chains to the same VK chain has no obvious bearing on the claims under examination, which would not appear to read on such antibodies.

Thus, Applicants respectfully maintain that, in the words of the Court cited by MPEP 2164.01, "one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." The application sets forth sequence information sufficient to permit the practitioner to make and use the invention in combination with information set forth in the invention disclosure. Thus, deposit of the materials discussed in the Action is not necessary to enable claim 6 or claim 22. Reconsideration and withdrawal of the rejection is respectfully requested.

2. Rejection of claims 1-40 and 33-40

Claims 1-40 and 33-40 are rejected under §112, first paragraph, as allegedly not enabled because the specification is allegedly not enabled for antibodies that have only a VH or a VL chain alone and which do not bind antibody different from that bound by the parent. Action, at page 8. According to the Action,

> [i]t is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions o a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope." . . . It is expected that all of the heavy and light chains in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Action, at page 9. Applicants traverse.

Applicants respectfully point out that this argument is completely unsupported and is based on what is allegedly well known in the art. In point of fact, however, the Action's argument is contrary to what was known in the art well before the priority date of the present invention.

Some three years before the priority date of the present invention, one of the co-inventors of the present specification demonstrated that a single chain of an antibody could successfully direct a cytotoxin to a target cell, and result in binding to and death of, the target cell. The report of the studies was published in one of the best known and most prestigious scientific journals, the Proceedings of the National Academy of Science. See, Kuan and Pastan, Proc Natl Acad Sci (USA) 93:974-978 (1996) (hereafter, "Kuan and Pastan," for the Examiner's

convenience, a copy of the Kuan and Pastan PNAS publication is attached). The Examiner's attention is respectfully directed to the bottom panel of Figure 1 of Kuan and Pastan, which diagrams the structure of the B1(V_H)-PE33 immunotoxin, which has just the heavy chain of the B1 antibody as the targeting agent. As shown in Table 1 (page 976, right column), cells which expressed the target antigen were killed by B1(V_H)-PE33 at IC_{50}s of only 2 and 4 ng/ml, while B1(V_H)-PE33 was not cytotoxic to cells negative for the target antigen at over 1000 ng/ml, or concentrations at least 250 times higher.

Kuan and Pastan therefore informed the art, almost two years before the priority date of the present application, that a VH or VL chain of an antibody, by itself, could successfully target immunoconjugates to target cells. The Action's contention that all the CDRs of both chains are required to produce a protein having antibody binding function is therefore simply incorrect. Persons of skill in the art were fully enabled to make the claimed antibodies and immunoconjugates without undue experimentation.

For extra measure, Applicants note that the results reported in Kuan and Pastan also resulted in the issuance of U.S. Patent 5,980,895 (a copy of the '895 patent is enclosed for the Examiner's convenience). Claim 19 of the '895 patent claims a single chain immunotoxin targeted by either a VH chain without the presence of a VL chain, or a VL chain without the presence of a VH chain. Thus, the Patent and Trademark Office has already officially recognized that a single chain of an antibody can be used as the targeting portion of an immunoconjugate.

The sole support for the Action's proposition is a publication by Rudikoff et al., PNAS 79:1979 (1982) ("Rudikoff"). Rudikoff is cited only to show that a change in one residue of a CDR resulted in loss of antigen-binding function. Action, at page 9. From this, the Action hypothesizes that "it is unlikely that antibodies that have only a VH or VL chain . . . which would contain less than the full complement of CDRs from the heavy and light variable regions of an antibody would have the required binding function." Id., at page 9-10, bridging sentence. Contrary to the Action's hypothesis, however, the results set forth in the Kuan and Pastan

reference and the '895 patent demonstrate that single chains alone retain antigen-binding capability.

In brief, the rejection is based on the unsupported assertion that both chains of an antibody are needed to make a intact antigen-binding site. The Kuan and Pastan reference establishes that, well prior to the priority date, persons of skill in the art were informed that a single chain of an antibody could successfully serve as the targeting portion of an immunoconjugate and result in both antigen-specific binding and cytotoxicity. This position has been officially recognized as enabled by the Patent and Trademark Office in the '895 patent. Reconsideration and withdrawal of the rejection are respectfully requested.

3. Rejection of claim 21

Claim 21 is rejected as broadly drawn to expressing mutated antibody polypeptides comprising a surface protein of a bacteriophage. According to the Action, the specification teaches expression of scFvs as fusions to the gIII protein of filamentous phage. The Action asserts that the specification does not teach fusions to any other phage surface protein nor evidence that antibody fusions to "just any phage surface protein" would result in the selection of high affinity antibodies. Action, at pages 10-11. Applicants amend in part and traverse.

To clarify the claim, claim 21 has been amended to recite that the polypeptide is expressed in conjunction with a phage surface protein.

Applicants respectfully traverse the rejection. As noted in Section C 1, above, the "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.". MPEP § 2164.01, *quoting, United States v. Telectronics, Inc.*,857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Phage display has been known in the art since at least the late 1980's, and a search of the PTO database shows that, as of the present date, over 2000 patents have issued which cite the term "phage display" in one of the search fields. Applicants further note that MPEP §2164.01 reminds the Examining Corps that "[a] patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802

F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987)" (Emphasis added.) Accordingly, in addition to the teachings of the specification, Applicants are entitled to rely on all of the teachings in the art regarding the use of phage display proteins to guide the practitioner in practicing phage display. Applicants therefore respectfully maintain that claim 21 is fully enabled as amended.

D. Rejection under 35 U.S.C. § 102(b) over Yelton

Claims 1-5, 8, 10, 21, 27, and 31 are rejected under 35 U.S.C. § 102(b) as anticipated by Yelton et al., J Immunol, 155:1994-2004 (1995) ("Yelton"). According to the Action, Yelton teaches affinity maturation of a monoclonal antibody using codon based mutagenesis including A/CNN and NNG/T. Applicants amend in part and traverse.

As amended, claims 1 and 27 recite that the amino acids mutated from those of the parental antibody are encoded by codons with a nucleotide within one of two recited hot spot motifs. It appears that Yelton, in contrast, simply introduced mutations at "each position within the targeted CDR region." Yelton, supra, at 1997, left column, bottom paragraph. The same paragraph makes clear that the NNG/T the Action assumes is a hot spot in the parental antibody (here, the one Yelton refers to as BR96) is in fact a nucleotide triplet introduced by the authors into the position to be mutated, not a codon appearing in the parental antibody.

Accordingly, Applicants respectfully maintain that the Action does not show that the reference sets forth each element of the claims as now amended. As the Examiner will recall, "[a] claim is anticipated only if each and every element as set forth in the claim is found...in a single prior art reference." MPEP 2131, citing *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, Applicants submit that Yelton does not constitute a proper reference against the claims, as amended, for purposes of finding anticipation under §102(b). Reconsideration and withdrawal of the rejection is respectfully requested.

E. Rejection under 35 U.S.C. § 102(e) over Marks

Claims 1-5, 8, 10, 12-14, 16, 21, 27, and 31 are rejected under § 102(e) as anticipated by Marks, U.S. Patent No. 5,977,322. ("Marks"). According to the Action, Marks mutated heavy and light chain CDRs using NNS nucleotides and increased affinity. Action, at pages 13-14. Applicants amend in part and traverse.

As amended, claims 1 and 27 recite that the amino acids mutated from those of the parental antibody are encoded by codons with a nucleotide within one of two recited hot spot motifs. It appears that Marks, in contrast, created libraries which introduced randomized mutations into a number of contiguous residues in CDRs (e.g., four libraries of four residues mutated in the VH CDR3 (Marks, column 60, lines 19-27) or 9 amino acids of VL CDR3 (id., col. 64, lines 15-21)).

As amended, claims 1 and 27 recite that the amino acids mutated from those of the parental antibody are encoded by codons with a nucleotide within one of two recited hot spot motifs. Accordingly, Applicants respectfully maintain that the Action does not show that the reference sets forth each element of the claims as now amended. As the Examiner will recall, "[a] claim is anticipated only if each and every element as set forth in the claim is found…in a single prior art reference." MPEP 2131, citing *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Thus, Applicants submit that Marks does not constitute a proper reference against the claims, as amended, for purposes of finding anticipation under §102(e). Reconsideration and withdrawal of the rejection is respectfully requested.

F. Rejection under 35 U.S.C. § 102(b) over Goyenechea

Claims 1 and 4 are rejected under 35 U.S.C. § 102(b) as anticipated by Goyenechea and Milstein, PNAS 93:13979-13984 (1996) ("Goyenechea"). According to the Action, page 13979 of Goyenechea teaches affinity maturation of antibody chains associated with hot spot sequence motifs comprising G/A-G-T/C-A/T and AGY (Action, at page 14), while page 13982 of the reference teaches amino acid substitutions that increased antibody affinity to 2-phenyloxazolone by factors of 8 and 10 fold. Action, at page 15. Applicants traverse.

The Action's statements about the teachings of Goyenechea are correct. They are, however, taken out of context. In context, it is clear that Goyenechea does not anticipate the claims. While Goyenechea does teach hot spots such as those recited in the present claims, the increases in affinity to 2-phenyloxazolone referenced in Goyenechea are not related to mutations in amino acids encoded by codons with nucleotides within hot spots recited in the claims.

The increase of antibody affinity to 2-phenyloxazolone discussed in Goyenechea refers to a substitution of His-34 by Asn or Gln during affinity maturation. Goyenechea's support for the assertion that the substitution of His-34 by these residues increases affinity by 10 or 8 fold, respectively, is a citation to a previous paper, reference 20, which the bibliography lists as Berek and Milstein, Immunological Rev 96:23-41 (1987) ("Berek and Milstein"; a copy of Berek and Milstein will be provided as soon as possible). A review of Figure 4 of Berek and Milstein, on page 32, shows the CDR of that includes His-34 as having the following amino acid and nucleotide sequences:

Residue numbers	33	34	36
Amino acid	Met	His	Tyr
Nucleotides	AUG	CAC	UAC

(The Examiner will note that Berek and Milstein's numbering of the residues in the CDRs, as shown in the Figure, is not continuous.)

A review of the nucleotide sequence of the codon encoding His-34 and its two adjacent residues indicates that His-34 is not encoded by nucleotides within an AGY hot spot or within a G/A-G-T/C-A/T hot spot. The teachings of Goyenechea relied on by the Action therefore do not teach increasing the affinity of an antibody by an amino acid substitution encoded by a codon that comprises a nucleotide belonging to a hot spot motif selected from AGY or RGYW, as recited by the claims under examination.

Accordingly, Applicants respectfully maintain that the Action does not show that the reference sets forth each element of the claims. As noted above in connection with the rejection of the claims as anticipated by Yelton, "[a] claim is anticipated only if each and every element as set forth in the claim is found…in a single prior art reference." MPEP 2131, citing *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.

1987). Thus, Goyenechea does not constitute a proper reference against the claims, as amended, for purposes of finding anticipation under §102(b). Reconsideration and withdrawal of the rejection is respectfully requested.

G. Rejection under 35 U.S.C. § 103(a) over Yelton

Claims 1-6, 8-21, 27, 28, 31-34, 36, 37, 39, and 40 are rejected under 35 U.S.C. § 103(a) as anticipated by Yelton, supra, in view of Chowdhury, PNAS 95:669-674 (1995)("Chowdhury (a)") and Chowdhury J Mol Biol 281:917-928 (1998)("Chowdhury (b)"). Applicants amend in part and traverse.

As amended, claims 1 and 27 recite that the amino acids mutated from those of the parental antibody are encoded by codons with a nucleotide within one of two recited hot spot motifs. As noted above in connection with the rejection under §102(b), it appears that Yelton simply introduced mutations at "each position within the targeted CDR region." Yelton, supra, at page 1997, left column, bottom paragraph. Yelton does not teach or suggest that the affinity of an antibody can be increased by mutating only the nucleotides encompassed by a hot spot motif, and therefore cannot render obvious antibodies improved by the method of the present invention. Moreover, the same paragraph of Yelton makes clear that the NNG/T the Action assumes is a hot spot in the parental antibody (the one Yelton refers to as BR96) is in fact a nucleotide triplet introduced by the authors into the position to be mutated, not a codon appearing in the parental antibody. To the extent the obviousness rejection relies on a teaching of Yelton to combine with the other references, therefore, it must be reconsidered and, Applicants believe, withdrawn.

The two Chowdhury references do not make up for the deficiencies in Yelton. Chowdhury (a) is cited merely because it teaches the SS antibody. Since Yelton does not show that even the antibody it discusses could have its affinity increased by mutations of nucleotides only in the hot spots regions, it provides no basis for showing that such an improvement could be expected with regard the SS antibody in particular. The citation of Chowdhury (b) appears even less helpful to the Action's argument. Chowdhury (b) does not relate to the SS antibody at all, but relates instead to an earlier-discovered anti-mesothelin antibody known as "K1". Moreover,

even with regard to the K1 antibody, Chowdhury (b) does not relate to increasing the affinity of the antibody, but rather to increasing its stability and yield. See, Chowdhury (b), abstract. Thus, Applicants respectfully submit Chowdhury (b) is not relevant to the claims under examination, alone or in combination with Yelton and Chowdhury (a).

Accordingly, Applicants respectfully maintain that this rejection fails to set forth a proper prima facie case of obviousness of the claims as now presented. Reconsideration and withdrawal of the rejection are respectfully requested.

H. Rejection under 35 U.S.C. § 103(a) over Marks

Claims 1-6, 8-21, 27, 28, 31-34, 36, 37, 39, and 40 are rejected under 35 U.S.C. § 103(a) as anticipated by Marks, supra, and further in view of Chowdhury (a) and Chowdhury (b). Applicants amend in part and traverse.

As noted in connection with the anticipation rejection, above, as amended, claims 1 and 27 recite that the amino acids mutated from those of the parental antibody are encoded by codons with a nucleotide within one of two recited hot spot motifs. It appears that Marks, in contrast, created libraries which introduced randomized mutations into a number of contiguous residues in CDRs (e.g., four libraries of four residues mutated in the VH CDR3 (Marks, column 60, lines 19-27) or 9 amino acids of VL CDR3 (id., col. 64, lines 15-21)). Marks does not teach or suggest that increases in the affinity of antibodies can be achieved by mutating nucleotides within the designated hot spots without also mutating other nucleotides. Marks therefore does not teach or suggest the invention as now claimed.

With regard to the claims that concern increasing the affinity of the SS antibody in particular, Applicants note that the SS antibody is reported by Chowdhury (a) to have very high affinity for mesothelin: 11 nM, or 11 x 10^{-9}M. See, Chowdhury (a), abstract. Marks does not show that an antibody such as SS which has already undergone multiple rounds of phage display selection for affinity can have its affinity further improved by mutation at the hot spots recited in the claims. Applicants submit that the practitioner would be just as likely to conclude that the antibodies selected by the phage display process, and displaying the affinity reported in

Chowdhury (a) had already undergone mutation at these hot spots and obtained whatever benefit was available from such mutations.

The two Chowdhury references do not make up for the deficiencies in Marks. Chowdhury (a) is cited by the rejection merely because it teaches the SS antibody. Since Marks does not show that antibodies could have their affinity increased by mutations of nucleotides only in the hot spots regions, it provides no basis for showing that such an improvement could be expected with regard the SS antibody in particular. Once again, the citation of Chowdhury (b) does not appear helpful to the Action's argument. Chowdhury (b) does not relate to the SS antibody at all, but relates instead to an earlier-discovered anti-mesothelin antibody known as "K1". Moreover, even with regard to the K1 antibody, Chowdhury (b) does not relate to increasing the affinity of the antibody, but rather to increasing its stability and yield. See, Chowdhury (b), abstract. Thus, Applicants respectfully submit Chowdhury (b) is not relevant to the claims under examination, alone or in combination with Marks and Chowdhury (a)

Accordingly, Applicants respectfully maintain that this rejection fails to set forth a proper prima facie case of obviousness of the claims as now presented. Reconsideration and withdrawal of the rejection are respectfully requested.

I. Rejection under 35 U.S.C. § 103(a) over Chowdhury (a) in view of Goyenechea

Claims 1-6, 8-21, 27, 28, 31-34, 36, 37, 39, and 40 are rejected under 35 U.S.C. § 103(a) as anticipated by Chowdhury (a) and further in view of Goyenechea and Adams et al., Cancer Res 58:485-490 (1998) ("Adams") and Marks. Action, at pages 22-24. Applicants amend in part and traverse.

Chowdhury (a) is cited because it teaches the SS antibody. The Action acknowledges that it does not teach hot spot sequence motifs. The Action alleges, however, that this deficiency is made up by Goyenechea, which the Action states teaches hot spot motifs and teaches that "antibody amino acid substitutions in hot spots that increase[] antibody affinity by [] factor[s] of 10 and 8." Action, at page 23. As shown above, however, Goyenechea in fact do not teach mutations in a hot spot motif recited in the claims that increase affinity. A review of the

underlying Beker and Milstein reference indicates that the mutations in His-34 that result in the increases in affinity cited by the Action do not result from mutations in the hot spot motifs recited in the claims. Accordingly, the premise of the Action's combination of Chowdhury (a) and Goyenechea does not survive scrutiny.

This deficiency is not made up by Adams. Adams is cited first for the proposition that increased affinity of antibodies leads to improved selective delivery of scFv antibodies. Action, at page 23. This is not in dispute. Adams is further cited for the proposition that scFvs that varied from each other by only one to three amino acid residues in the CDR3 differed in affinity for the same antigen by 320-fold. Action, at pages 23-24, bridging sentence. The Action does not allege, however, that Adams teaches that mutations in amino acids encoded by nucleotides within hot spots are advantageous for increasing affinity. It therefore does not teach or suggest the invention as claimed, alone or in combination with the first two references.

Marks is added to this mix to provide the basis for asserting that there is motivation to use the methods allegedly taught by Chowdhury (a), Goyenechea, and Adams for making scFv, Fab, $F(ab)_2$, dsFv, and diabodies conjugated to toxins. Action, at page 26. This does nothing to show that mutating nucleotides within the recited hot spots will result in increased affinity.

Marks is also alleged to show CDR randomization, and CDR residues 92, 93, and 94 were found to be associated with higher affinity antibodies when mutated. *Id.* This is not completely correct. As noted earlier, Marks et al. mutated 9 residues of the VL CDR3. See, Marks, col. 64, lines 15-20. In the third round of selection, several sFv were found with higher affinity than the wild type antibody, and of these, the most common mutation was at residue 92. Marks, at col. 64, lines 63-67. Marks then states that, in the fourth round of selection, six sFvs were identified, and none of these sequences were observed in the sFv sequenced from the third round. *Id.* at col. 65, lines 6-8. Significant sequence variation was noted at residues 93, 94, and less variability at residues 95 and 95a. *Id.*, at lines 22-26. col. 65. Thus, it is not clear from the text that, in the fourth round of selection, residue 92 had a mutation at the same time as residues 93 and 94 and, in any event, two other residues are also often mutated.

Applicants note, first, that the SS antibody is reported by Chowdhury (a) to have very high affinity for mesothelin: 11 nM, or 11 x 10^{-9}M. See, Chowdhury (a), abstract. Marks does not show that an antibody such as SS which has already undergone multiple rounds of phage display selection for affinity can have its affinity further improved by mutation at the hot spots recited in the claims. Applicants submit that the practitioner would be just as likely to conclude that the antibodies selected by the phage display process, and displaying the affinity reported in Chowdhury (a) had already undergone mutation at these hot spots and obtained whatever benefit was available from such mutations. Thus, with regard to the claims concerning improving the affinity of the SS antibody in particular, Applicants submit that Marks does not teach or suggest the invention as claimed.

Applicants further note that the Action fails to show a nexus between the teachings of Marks and the claims as recited. The Action fails to show that any of the mutations discussed in Marks are of amino acids encoded by codons with nucleotides encompassed by a hot spot motif as recited in the claims. The Applicants respectfully remind the Examiner that the Examiner has the initial burden to present a prima facie case of obviousness, and that the burden does not shift to the Applicant until and unless that prima facie case has been made. Applicants respectfully point out that the Action fails to point to anything in Marks showing that the mutations it discusses fall within the scope of the claims as presented. Moreover, since it is unlikely all 4 of the residues mutated in the fourth round of selection in Marks happen to be encoded by codons with nucleotides encompassed by a hot spot motif, it is unclear why the practitioner would be guided by Marks to mutate only residues within such a hot spot, except in hindsight using the present disclosure as a guide.

In sum, Applicants respectfully submit Chowdhury (a), alone or in combination with Goyenechea, Adams and Marks, fails to set forth a proper prima facie case of obviousness of the claims as now presented. Reconsideration and withdrawal of the rejection are respectfully requested.

J. Rejection under 35 U.S.C. § 103(a) over Chowdhury (a) in view of Wagner

Claims 1-6, 8-21, 27, 28, 31-34, 36, 37, 39, and 40 are rejected under § 103(a) as anticipated by Chowdhury (a) and further in view of Wagner et al., Nature 376:732 (1995) ("Wagner"), Pasten et al., U.S. Patent No. 6,083,502 ("Pastan"), and Adams. Action, at pages 27-32. Applicants amend in part and traverse.

Chowdhury (a) is cited because it teaches the SS antibody. Once again, the Action acknowledges that Chowdhury (a) does not teach hot spot sequence motifs. The Action alleges, however, that this deficiency is made up by Wagner and by Pastan. According to the Action, Wagner teaches the hot spot serine codon AGY and the hot spot motif A/G G C/T A/T, as preferred mutations during affinity maturation and that "biased" serine mutations have evolved to help somatic hypermutation target CDRs rather than framework regions and thus target residues that might increase affinity rather than destroy framework regions. Action, at page 28.

The combination of Chowdhury (a) and Wagner, however, does not teach or suggest the present invention. The fact is that Chowdhury (a) reports that the SS antibody already has a high affinity for the mesothelin antigen. Indeed, the reference reports that SS has a Kd of 11 nm, that is, 11 x 10^{-9}M. See, Chowdhury (a), abstract. The fact that Wagner teaches natural antibodies undergo increases in antibody affinity during the natural maturation process, or that this maturation takes place due to mutations localized in the CDRs does not teach or suggest that an antibody which has already undergone multiple rounds of phage display selection for affinity can have its affinity further improved by mutation at the hot spots recited in the claims. The practitioner would be just as likely to conclude that the antibodies selected by the phage display process, and displaying the affinity reported in Chowdhury (a) had already undergone mutation at these hot spots and obtained whatever benefit was available from such mutations.

The Pastan patent does not make up this deficiency. Pastan is cited because it reports that the K1 antibody can be used to target various kinds of toxins to mesothelin-expressing cells. It does not teach or suggest that the SS antibody, having already undergone

multiple rounds of phage display selection for affinity, could have its affinity further improved by mutation at the hot spots recited in the claims.

The deficiencies noted above are not made up by Adams. The rejection does not make a new argument about the effect of Adams, Action at page 28, last line; rather, it relies on the discussion of Adams set forth in connection with the earlier rejections. *Id.* Therefore, the points made above in connection with Adams are appropriate here as well. As pointed out above, Adams is cited for two propositions: first, that increased affinity of antibodies leads to improved selective delivery of scFv antibodies, which is not in dispute, and second, that scFvs that varied from each other by only one to three amino acid residues in the CDR3 differed in affinity for the same antigen by 320-fold. As noted above, however, the Action does not allege, however, that Adams teaches that mutations in amino acids encoded by nucleotides within hot spots are advantageous for increasing affinity. It therefore does not teach or suggest the invention as claimed, alone or in combination with the other references.

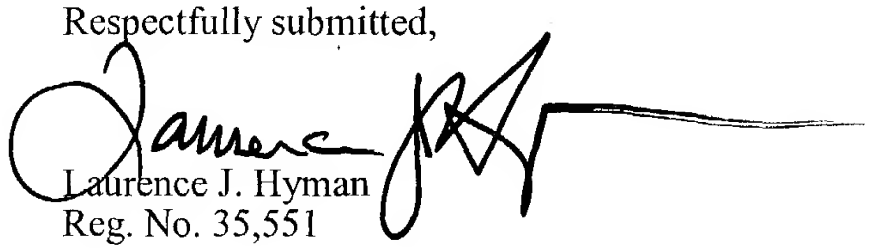
In sum, Applicants respectfully submit Chowdhury (a), alone or in combination with Wagner, Pastan, Adams and Marks, fails to set forth a proper prima facie case of obviousness of the claims as presented. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, he is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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